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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,519	05/01/2002	Audrey Goddard	P3230R1C001-168	8149

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/063,519	**Applicant(s)** GODDARD ET AL.	
	Examiner David J. Blanchard	**Art Unit** 1643	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 1-5.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 9/6/05
13. ☐ Other: _____.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: The response filed 9/6/2005 has been carefully considered, but does not overcome the utility and lack of enablement rejections of record. Applicant reviews the evidentiary standard regarding the legal presumption of utility. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Applicant argues that the standard for utility is not absolute certainty and based on the evidence submitted, applicant asserts that it is more likely than not that a person of ordinary skill in the art would be convinced to a reasonable probability, that the asserted diagnostic and therapeutic utilities of the claimed antibodies are true. In response to these arguments the rejection does not question the presumption of truth, or credibility, of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides and antibodies thereto are credible and specific, however, they are not substantial. The data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO1864 polypeptide nor any particular biological activity of the polypeptide to which the claimed antibody binds. Given the totality of the evidence of record, contrary to applicant's arguments, it is not established in the art that the accepted understanding is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. The accepted understanding in the art is that there are distinct regulatory factors at the transcriptional and translation levels of expression. The literature of record supports that RNA expression cannot inevitably be correlated with levels of the encoded polypeptide and one skilled in the art would not assume that the levels of RNA are predictive of the levels of the encoded polypeptide given the distinct regulation of transcription and translation. Applicant appears to have acknowledged this in the response at page 16, stating that there are many factors that determine translational efficiency for a given transcript, or the half-life of the encoded protein. Thus, one of skill in the art would understand that there are many factors that are independent of the level of mRNA expression and would determine the levels of the corresponding protein. Applicant has not provided any evidence of PRO1864 polypeptide expression and one skilled in the art would be required to do further research to determine whether or not the PRO1864 polypeptide was over-expressed in melanoma samples versus normal skin. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. For these reasons and the reasons of record, the rejection is maintained.

With respect to the rejection of claims 1-5 for lack of enablement, the response filed 9/6/2005 has been carefully considered, but is deemed not to be persuasive. Applicant again argues that the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. The evidence of record indicates that the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors effecting transcription and translation. Indeed the evidence submitted in the IDS filed 9/6/05 provides additional supporting evince for this fact. For example, Hanash S. [a] (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005, IDS reference 9) recently stated "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash [a] teaches that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Additionally, Hanash et al [b] (The Pharmacogenomics Journal, 3(6):308-311, 2003, Ids reference 8) states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). According to Hanash et al [b], there is a need to assay protein levels and activities and numerous alterations may occur in proteins that are not reflected in changes at the RNA level (see page 311). Clearly, contrary to applicant's arguments and as evidenced by the art above and that already of record, it is not established in the art that the accepted understanding is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. The literature supports that RNA expression cannot inevitably be correlated with levels of the encoded polypeptide and one skilled in the art would not assume that the levels of RNA are predictive of the levels of the encoded polypeptide given the distinct regulation of transcription and translation. Thus, one of skill in the art would not be able to predictably practice the claimed antibodies as a diagnostic or therapeutic agent absent evidence and exemplary guidance that the PRO1864 polypeptide is over-expressed in melanomas relative to normal skin. For these reasons the rejection is maintained.

Respectfully,
David J. Blanchard
571-272-0827

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